REMARKS

Amendments to the Specification

The specification has been amended as shown above to correct a typographical error inadvertently transposing two amino acid residues. This typographical error was previously corrected in the claims in a Preliminary Amendment filed March 20, 2002. Support of the amendments can be found throughout the specification as filed, for example on page 7, line 27 and Table 2, SBS# 293 (SEQ ID NO:705).

Status of the Claims

Claims 1 to 49 are pending and stand subject to a 90-way restriction requirement, addressed below. Claim 1 has been amended as shown above to make explicit what was previously implicit, namely that the zinc finger proteins as claimed are non-naturally occurring. *See, e.g.,* page 13, lines 28-29 of the specification. Thus, claims 1-49 are pending as shown above.

Restriction Requirement

The Examiner has restricted the claims into 90 allegedly distinct inventions as follows:

Groups 1-45 (pending claims 1-46) drawn to zinc finger polypeptides, class 530, subclass 300); and

Groups 46-90 (pending claims 47-49), drawn to polynucleotides encoding zinc finger polypeptides, class 536, subclass 23.1.

Applicants provisionally elect DRSNLTR for F1; TSGHLSR for F2; and RSDHLSR for F3, **with traverse**.

First and foremost, Applicants traverse on the grounds that it is entirely incorrect and improper to assert that there are 90 inventions (45 distinct inventions in claims 1-46 and 45 distinct inventions in claims 47-49). The Patent Office's own rules are clear that the Office should not refuse to examine that which applicants regard as their invention. *See, e.g.,* M.P.E.P. § 803.02.

In the pending case, Applicants submit that the Office has improperly refused to examine as a whole that which they regard as their invention. Applicants' claimed invention clearly necessitates the recitation of multiple sequences inasmuch as it is drawn to zinc finger proteins (or polynucleotides encoding these proteins) that recognize a target site of the form GNNGNNGNN. Plainly, Applicants regard their invention as including a number of multi-finger

proteins, wherein each finger of a multi-finger protein binds to a GNN target subsite, and the amino acid sequence of the finger depends on the nucleotide sequence of the subsite. As such, it is entirely improper for the Office to parse the pending claim into 90 different inventions. Given the nature of the pending claims, Applicants submit that the restriction requirement cannot be applied or maintained and, moreover, that such restriction prevents Applicants from clearly and distinctly claiming their invention.

In support of the restriction requirement, the Examiner asserts that the claims of each of the 90 groups are allegedly patentably distinct. However, Applicants note that two criteria must be met for a proper restriction requirement under M.P.E.P. § 803: (1) the inventions must be independent or [*sic*] distinct as claimed; and, in addition, (2) there must be a serious burden on the Examiner if restriction is not required. Applicants respectfully submit that the Examiner has not met the burden of demonstrating that both criteria have been met.

In support of restriction among 45 different amino acid sequences, the Examiner asserts that the different sequences "differ in structure and in function, *i.e.*, binding to different S target sites." (Restriction Requirement, pages 2-3). Likewise, the 45 different polynucleotide sequences encompassed by claims 47-49 are also alleged to differ in structure and function. *Id.* In fact, all claimed amino acid sequences have the same structure (three-fingered, non-naturally occurring zinc finger protein in which each zinc finger comprises a sequence of seven-amino acid residues involved in binding to DNA), as described for example on page 9, lines 4-6; page 15, lines 5-7 and page 16, line 28 through page 18, line 5. Moreover, all claimed amino acid sequences have the same function (DNA binding), as described for example on page 11, lines 16-18; on page 14, line 10 and on page 15, lines 7-9. Similarly, all claimed polynucleotides have the same structure (sequences that encode a three-fingered, non-naturally occurring zinc finger protein in which each zinc finger comprises a sequence of seven-amino acid residues involved in binding to DNA) and same function (encoding a zinc finger protein that binds DNA). Thus, Applicants submit that the Restriction Requirement cannot be sustained as between the claims of Groups 1-45 (claims 1-46) or between the claims of Groups 46-90 (claims 47-49). The record establishes that the amino acid sequences should be examined together and that the polynucleotide sequences should also be examined together since, for both the claimed amino acid sequences and the claimed polynucleotides, common structure and function are present.

Turning to the restriction between proteins and polynucleotides, Applicants submit that the Examiner has not demonstrated that the protein claims of Groups 1-45 are distinct from the polynucleotide claims of Groups 46-90. In particular, the Examiner acknowledges that Groups 1-45 and 46-90 are related but nonetheless states "they are distinct inventions because the protein product can be made by another and materially different process, such as by synthetic peptide

synthesis or purification from a natural source." (Restriction Requirement, page 4). However, Applicants note that the claimed proteins comprise three zinc fingers (claim 1, lines 1-3) and, since a single zinc finger contains approximately 30 amino acids (as disclosed, for example, at page 1, lines 20-21 and at page 16, line 28 and well-known to those of skill in the art), a three-finger protein comprises at least 90 amino acids[1]. *See* also page 17, lines 21-23 and SEQ ID NOs:13 and 15. It is well known that peptide synthesis techniques are not routinely capable of generating oligopeptides of this length that are readily purified or that are known to form functional tertiary structures. *See, e.g.,* Gelinksy et al. (2002) *Eur. J. Inorg. Chem.* 2458-2462 (copy attached hereto), in which the authors state that the maximum peptide length for which clean chromatographic separation can be obtained is 25-30 amino acid residues. Accordingly, the Office's assertion that the claimed protein products can be made by other materially different processes is untenable.

Furthermore, inasmuch as the claimed proteins are nonnaturally occurring zinc finger proteins (claims 1-46 and page 13, lines 28-29), under no circumstances would it be possible for them to be purified from a natural source. Thus, the Office's assertion that the claimed proteins could be purified from a natural source is also incorrect.[2]

If the Restriction Requirement is maintained for these reasons, Applicants respectfully request: (1) that the Office provide evidence that peptides longer than 90 amino acids could be generated, in high yield and purity, by techniques of automated synthesis that were available at the time the application was filed, and (2) identify a natural source of the claimed proteins and nucleic acids.

In addition, the Office also errs in asserting that "the DNA may be used for processes other than the production of the protein, *such as nucleic acid hybridization*." (Restriction Requirement, page 3, emphasis added). Applicants respectfully remind the Office that the claimed polynucleotides encode non-naturally-occurring proteins. *See*, for example, the specification at page 13, line 28-29. Thus, it is difficult to imagine what could be detected in a hybridization assay that uses a polynucleotide encoding a non-naturally occurring protein as a probe. What would be the target of such a hypothetical hybridization assay? Accordingly, Applicants believe that the utilities asserted by the Office for Groups 1-90 are not specific, substantial or credible, but are merely "throwaway" utilities used to support an attempt to improperly restrict the claimed subject matter. Applicants respectfully remind the Office of the criteria for utility (66 Fed. Reg. 1092, 1098) and expect that the same criteria would apply to

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1 Not including any functional domain which may be a part of the protein (see, *e.g.*, claim 46)

2 For the same reason, it would also be impossible to purify the claimed polynucleotides from a natural source.

hypothetical utilities used by the Office to support a contention of distinctness between certain groups of claims.

In fact, both the claimed polypeptides of Groups 1-45, and the polynucleotides of Group 46-90, can be used in the same method, namely modulation of gene expression, as taught throughout the specification. Thus, if the restriction is maintained, Applicants request that the Office explicitly identify specific and substantial utilities, that would be credible to one of skill in the art, for these alleged different "inventions," and provide evidence that one of skill in the art would have recognized that the use of a polynucleotide encoding a non-naturally-occurring polypeptide in a hybridization assay was established as of the filing date of the present application. Applicants also request that the Office specifically identify the target(s) of such hypothetical hybridization assays.

Applicants also traverse on the grounds that it would not be unduly burdensome to search the allegedly distinct inventions together. In fact, for the reasons noted above, it is required that multiple sequences be searched together. A search for any combination of F1, F2 and F3 zinc fingers would necessarily reveal art relevant to each of the allegedly distinct "inventions." It would, therefore, not be burdensome (and even save the Office time and resources) to examine the claims together. Because the subject matter of all pending claims is related in both structure and function, there is no burden (let alone a serious burden) on the Examiner in searching and examining them together. Applicants reiterate that the polypeptides of Groups 1-45 and encoded by Groups 46-90 all have the same structure (three fingered zinc finger proteins, where each finger comprises a septa-peptide sequence that binds to DNA) and the same functions (DNA binding). Again, examining the groups together would save the Office time and effort, as a search for one group would necessarily reveal art relevant to the other groups.

In sum, the Examiner has not shown that it would impart a serious burden to examine all the claims together. Examination of these claims in one application would not place an undue burden on the Examiner, but would, in fact, actually save the Examiner time. In light of the Office's concerns about increasing numbers of applications, examination of the pending claims in a single application (rather than in ninety separate applications) would also save Patent Office resources.

Applicants expressly reserve their right under 35 USC §121 to file one or more divisional applications directed to the nonelected subject matter during the pendency of this application.

In view of the foregoing remarks, Applicants respectfully submit that the restriction requirement be withdrawn. Should the Examiner instead choose to make this restriction requirement FINAL, Applicants reserve their right, pursuant to 37 C.F.R. §§ 1.144 and 1.181, to petition this requirement at any time during the pendency of this application, prior to appeal.

Respectfully submitted,

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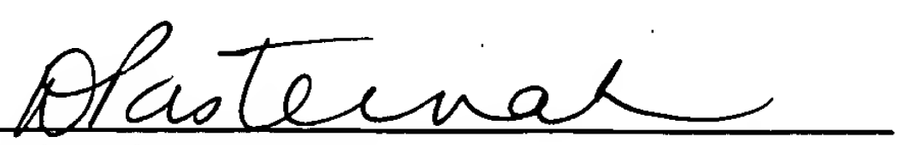
By: 
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